Influence of Atropine and of Vagally Mediated Bradycardia on the Occurrence of Ventricular Arrhythmias following Acute Coronary Occlusion in Closed-Chest Dogs

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SUMMARY

In contrast to previous opinions, recent investigations have suggested that increasing heart rate (HR) with atropine when moderate sinus bradycardia accompanies acute myocardial infarction is not necessarily beneficial. To further characterize the influence of vagally mediated changes in HR during ischemia, we evaluated the effects of atropine and of electric stimulation of the vagus nerves on the incidence of ventricular arrhythmias during acute coronary occlusion in closed-chest dogs. Protection from occlusion-induced arrhythmia was not observed when 28 dogs receiving atropine were compared with 27 control dogs. Rather, the total incidence of ventricular arrhythmias was significantly higher (P < 0.05) and ventricular fibrillation tended to occur more frequently in the atropine-treated group. Moreover, fewer ventricular arrhythmias (and total absence of ventricular fibrillation or close-coupled premature beats) were noted in 12 control animals with spontaneous bradycardia (HR < 60 beats/min) compared with 15 nonbradycardic animals. When vagal stimulation produced bradycardia (HR = 40–60 beats/min) during coronary occlusion, occurrence and character of ventricular arrhythmias were the same as in dogs with normal rates (HR = 80–100 beats/min). Although these results may not necessarily apply to man, further studies are needed before it can be assumed that all individuals with moderate bradycardia during acute myocardial infarction should receive vagolytic agents.

Additional Indexing Words:
Vagal stimulation Ventricular fibrillation Myocardial infarction Arrhythmia prophylaxis Sudden death

RECENT OBSERVATIONS have emphasized that atropine-responsive bradycardia (i.e. HR ≤ 60 beats/min) is frequently found in patients examined soon after developing symptoms of acute myocardial infarction.1-4 The clinical significance of this vagally mediated bradycardia remains uncertain. Undoubtedly, extreme bradycardia of any etiology can lead to severe compromise of hemodynamic function. However, it has been suggested that even moderate bradycardia, occurring in a patient who is otherwise stable, may predispose to serious ventricular arrhythmias.5-7 This concept implies that speeding the heart rate with a vagolytic agent such as atropine is appropriate for all individuals with bradycardia during the early phases of acute myocardial infarction to protect against electrical instability.5, 8-10

A growing body of evidence, however, suggests that this line of reasoning may not be correct. In a recent evaluation of 765 patients hospitalized with acute myocardial infarction,11 those 152 individuals with periods of sinus bradycardia (76% never received atropine; Norris RM: Personal communication) actually had a considerably lower mortality rate than those with heart rates between 60 and 100 beats/min. Moreover, when ventricular fibrillation developed in seven members of the bradycardia group with known prefrillation sinus rates, it was always preceded by sinus rhythm at normal heart
rates, never by bradycardia. Furthermore, electrophysiologic studies of ischemic canine myocardium,\textsuperscript{12} in contrast to previous studies of normal myocardium,\textsuperscript{13} have shown that slower heart rates are accompanied by more homogeneous recovery of excitability and higher ventricular fibrillation thresholds, changes associated with greater electrical stability of the myocardium.

To further characterize the influence of vagally mediated changes in heart rate during the earliest phases of acute myocardial infarction, we compared the incidence of ventricular arrhythmias in closed-chest dogs subjected to coronary occlusion under control conditions with the frequency of arrhythmias in a similar group of animals in which a moderate blockade of vagal activity was produced by atropine. In a second group of animals with acute coronary occlusion, the incidence of ventricular arrhythmias was compared in dogs with normal heart rates and in those with moderate bradycardia produced by electrical stimulation of the vagus nerves.

Methods

Preparations

Six to 10 days prior to definitive study an inflatable balloon cuff was placed around a proximal portion of the left anterior descending coronary artery of mongrel dogs weighing 16–23 kg. For all dogs in the atropine studies and 15 of 50 dogs in the vagal stimulation studies operative technics were identical to those described previously.\textsuperscript{14} This included ligation of grossly evident intercoronary collateral vessels, a step designed to maximize the ischemia produced by balloon cuff inflation. In 35 dogs participating in vagal stimulation studies, however, ligation of these intercoronary collateral vessels was omitted. At the time of balloon cuff placement, atrial and (in the vagal stimulation series) ventricular epicardial monitoring electrodes were sewn in place and leads were brought to the skin surface together with a hollow tube communicating with the lumen of the balloon cuff.

Atropine Studies

Of the 55 dogs studied, each had resting heart rates below 90 beats/min prior to administration of any medication (studies were deferred when heart rate was in excess of 90 beats/min). Animals were sedated with 40 mg morphine sulfate and 15 mg diazepam i.m. and continuous electrocardiographic monitoring was instituted using limb leads II and aVF and the atrial epicardial electrode. The coronary artery was occluded by inflating the balloon cuff. After 10 min of occlusion those dogs randomly selected for treatment received a bolus of 0.16 mg atropine in its commercial solvent i.v., a dose sufficient to raise heart rate an average of 21 beats/min. Atropine was subsequently infused to maintain heart rate between 90 and 120 beats/min; in each dog heart rate was held within a 10–15 beat/min range. Control animals received small volumes of saline comparable to those given the treated dogs.

Sedation was maintained during the course of the study by additional intravenous diazepam 5–10 mg. There was no difference in diazepam requirements between the control and treated dogs. Continuous cuff inflation was assured by monitoring balloon pressure. After 1 hour of occlusion the cuff was suddenly deflated to evaluate the occurrence of arrhythmias during reperfusion. Ten minutes later the cuff was reinflated and the vessel occluded an additional 2 hours with continuing electrocardiographic monitoring and with maintenance of the heart rate in the atropine-treated dogs. Usually, arrhythmias appearing after reocclusion had already been noted during the initial hour of occlusion.

Vagal Stimulation Studies

On the day of definitive study the previously instrumented dogs were sedated with 40 mg i.m. morphine sulfate and 30 mg i.v. diazepam (a higher sedative dose was required in this group of studies because of the greater extent of the operative procedures. The cervical vagi were then exposed (without local anesthesia) and connected to a battery-powered electrical stimulator (Medtronics Inc, Minneapolis, Minn.). Femoral artery pressure, obtained via a percutaneous catheter, pressure within the balloon cuff, and the electrocardiogram were monitored throughout the study. Occlusion of the left anterior descending coronary artery was produced by cuff inflation. After 5 min of occlusion S-T-segment elevation in the ventricular lead (and usually in the limb leads as well) indicated acute ischemia in 96% of animals.

Ten minutes after initiating occlusion animals were randomly assigned to bradycardia (40–60 beats/min) or normal heart rate (80–100 beats/min) groups. Prior to randomization dogs were separated into those with spontaneous 10-min postocclusion heart rates < 90 and those with heart rates \( \geq 90 \) beats/min. Randomization then proceeded independently within each spontaneous heart rate grouping. In this way the random allocation was structured so that dogs in each treatment category had comparable spontaneous heart rates prior to vagal stimulation. Just before randomization vagal responsiveness was confirmed in each animal by briefly stimulating the vagus to reduce heart rate below 60 beats/min.

From 10 min after onset of occlusion until termination of the study 1 hour later, heart rate in the 24 dogs of the bradycardia group was held continuously between 40 and 60 beats/min by electrical stimulation of the right and, if necessary, the left vagus nerves. Using a pulse duration of 0.3 msec, mean stimulus parameters were approximately 4 v and 40 Hz with maximal values of 8 v and 80 Hz. However, the stimulus voltage and frequency necessary to maintain heart rate within the specified range varied greatly from dog to dog and also during the course of an experiment on a single dog.

Although sinus bradycardia was the typical response, vagal stimulation also elicited slow junctional escape rhythms and varying degrees of heart block. Despite the
reduced heart rate and the myocardial ischemia, systolic blood pressure uniformly remained essentially normal (90-150 mm Hg). Diastolic blood pressure decreased as low as 40 mm Hg in a few instances, but generally remained above 60 mm Hg.

Of the 26 dogs in the nonbradycardia group heart rate was maintained between 80 and 100 beats/min by electrical stimulation of the vagi in 17 and by atrial pacing in four. Heart rates of the remaining five dogs remained spontaneously between 80 and 100 beats/min.

Sedation was maintained throughout the remainder of the study by small intravenous doses of morphine sulfate and diazepam. Total dose of sedating drugs for the entire experiment averaged 50 mg morphine sulfate and 64 mg diazepam for the bradycardia group and 47 mg morphine sulfate and 53 mg diazepam for the normal heart rate group. These differences were not statistically significant.

After occlusion had been maintained for 1 hour (and heart rate controlled for 50 min), the balloon cuff was deflated and the arrhythmicogenic effects of reperfusion were observed until termination of the study 10 min later. Heart rate control was continued and the electrocardiogram and blood pressure monitored throughout this reperfusion period.

Analysis of Arrhythmias

In all animals the electrocardiographic signal was tape recorded and time coded to permit detailed review of the events observed. An arrhythmia was considered to be present during any 1 min if four or more ventricular premature contractions (VPCs) appeared singly or if two or more VPCs occurred consecutively. Ventricular tachycardia (VT) was defined as three consecutive VPCs with a coupling interval (R-R') of less than 1 sec. Except as noted subsequently (fig. 9) all arrhythmias developing prior to 10 min after occlusion (when atropine or heart rate control were initiated) were excluded in assessing arrhythmia incidence. In our preparation ventricular fibrillation (VF) never occurred before 10 min of occlusion.

Both clinical15–17 and experimental14, 18 studies have indicated that more closely coupled VPCs are more likely to be followed by ventricular fibrillation. Drawing on our aggregate experience with 102 closed-chest dogs developing ventricular arrhythmias (VPC and/or VT) with acute coronary occlusion,14 we found that 42% (34/81) of animals with R-R' below 0.43 sec subsequently developed VF within 2 hours. In marked contrast, none of the 21 dogs with R-R' of 0.43 sec or greater went on to VF when observed for the same time period. We consequently have used an R-R' of 0.43 sec in the present study to separate those close-coupled arrhythmias, which in our experience, are frequent harbingers of VF, from those ventricular arrhythmias with longer R-R', which appear to rarely (if ever) portend a fatal outcome. Dogs were classified on the basis of the ventricular arrhythmia with the lowest value of R-R': a dog was considered to have a "benign" (long R-R') arrhythmia only in the total absence of accompanying "malignant" (short R-R') arrhythmia.

Classification by R-R' was performed separately for arrhythmias occurring during occlusion and for arrhythmias occurring after release of occlusion. All animals with VF during occlusion were excluded in calculating the incidence of release arrhythmias. Of the 105 animals in this study only three with occlusion arrhythmias failed to manifest release arrhythmias, but 16 with release arrhythmias had no antecedent occlusion arrhythmias.

Statistical analysis of results was performed using a one-tailed interpretation of chi-square calculations, or where appropriate, direct probability calculations from 2 × 2 contingency tables.19 In one instance, noted subsequently, we employed a cumulative probability calculation, as described by Mantel and Haentzel.20

Results

Atropine Studies

As shown in table 1, dogs in both control and atropine-treated groups manifested a significant (CP < 0.01) rise in heart rate after coronary occlusion, a characteristic response of closed-chest dogs to myocardial ischemia produced in this manner. The magnitude of the change did not differ consistently in the two groups. Fifty minutes later, heart rate in the control group fell to preocclusion values, but heart rate in the treated group was maintained by atropine an average of 21 beats/min above the 10-min postocclusion rate throughout this 50-min period.

Data relating to the incidence and type of ventricular arrhythmias observed is given in figure 1. Atropine was never clearly protective and, in several categories, it was actually associated with a significantly increased incidence of arrhythmia. For example, a significantly higher total incidence of occlusion arrhythmias occurred in the treatment group (26/28 = 93%) when compared with controls (13/27 = 48%). Similarly, the total incidence of either occlusion or release arrhythmias was significantly higher in the atropine-treated animals. VF tended to occur at least twice as often in each subgroup of the treated animals. The number of animals involved was small, however, so that this deleterious tendency achieved only borderline significance (0.05 < P < 0.1) even in the summary category. Nevertheless, it is clear that atropine did not play a protective role.

A more detailed examination of our data revealed that pretreatment (i.e. 10-min postocclusion) heart rate exerted a powerful influence on the frequency of ventricular arrhythmias developing during the subsequent 50 min of occlusion. This influence was evident in several different ways. For example, figure 2 demonstrates that the incidence of the more
Incidence of each type of ventricular arrhythmia occurring during acute coronary occlusion (upper panel), following release of occlusion (middle panel), and occurring during either occlusion or release periods (lower panel). LONG R-R' = minimum coupling interval of VPC's or VT > 0.43 sec, SHORT R-R' = minimum coupling interval < 0.43 sec; VF = ventricular fibrillation. Each dog is categorized according to the most serious arrhythmia manifested (long R-R' < short R-R' < VF). P values are shown for all differences attaining or approaching significance. Number of animals in each category appears at bottom of corresponding bar.

Incidence of the more serious occlusion arrhythmias (VPC's or VT with R-R' < 0.43 sec or VF) when dogs are subdivided according to whether heart rate 10 min after coronary occlusion (and prior to atropine) was < 85 or ≥ 85 beats/min. Number of dogs in each category is shown at the bottom of the corresponding bar. Control dogs (leftward pair), atropine-treated dogs (middle pair), and the combination of control and treated dogs (rightward pair) each manifested a significantly increased incidence of serious arrhythmias in the ≥ 85 subcategory. Mean heart rate was 70 ± (SE) beats/min for all dogs < 85 and was 102 ± 3 for all dogs ≥ 85.

Progressively from 20% for animals with rates below 60 beats/min to 80% for animals with rates above 100 beats/min.

Evaluation of those 12 of 27 control dogs manifesting heart rates below 60 beats/min during occlusion (five dogs at 10 min postocclusion, seven additional dogs during the subsequent 50 min) suggests that bradycardia at any time during the occlusion period was associated with a decreased incidence of ventricular arrhythmia. As illustrated in figure 4, only two of 12 (17%) dogs with bradycardia developed occlusion arrhythmias; in each instance this arrhythmia was of the less serious variety. In contrast 11 of 15 (73%) of control dogs without bradycardia developed arrhythmias and, of these, eight (53%) were in the more serious category (six had short R-R' VPC or VT, two had VF).

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rate at 10 min of occlusion (prior to atropine administration) and evaluated the influence of treatment on the frequency of arrhythmias within each heart rate group (fig. 5). The data for the control dogs are the same as that represented in figure 3. Within every group occlusion arrhythmias tended to occur more often in treatment than in control dogs with comparable 10-min postocclusion heart rates. The number of dogs within each heart rate group was too small for independent statistical analysis. However, a statistical technic which cumulated the probabilities in each group (the Mantel-Haentzel test) did show a significantly greater incidence (P < 0.05) of occlusion arrhythmias in dogs receiving atropine when compared with that of controls matched for the 10-min postocclusion heart rate. A similar deleterious trend was associated with atropine administration when broader heart rate categories were used (fig. 2). In dogs with 10-min postocclusion heart rates ≥ 85 beats/min, the greater incidence of more serious occlusion arrhythmias was statistically significant (second bar compared with fourth bar, fig. 2).

Since heart rate itself appeared to be an important risk factor in the development of ventricular arrhythmias, we divided both control and treatment dogs into groups based upon heart rate.

**Figure 3**
Total incidence of occlusion arrhythmias in control animals as a function of heart rate measured after 10 min of coronary occlusion. Each open circle represents the arrhythmia incidence of the corresponding 10 beats/min subgroups shown on the horizontal axis. Frequency of arrhythmia rose in an approximately linear fashion with increasing 10-min postocclusion heart rate.

**Figure 4**
Incidence of less serious (LONG R-R' = coupling interval of VFC's or VT ≥ 0.43 sec), more serious (VF + SHORT R-R' = coupling interval < 0.43 sec), and lethal occlusion arrhythmias (VF) in 12 control dogs with atropine and 15 control dogs without atropine. Those dogs with bradycardia never developed more serious arrhythmias.

**Figure 5**
Total incidence of occlusion arrhythmias in control (light gray) and atropine-treated (dark gray) dogs as a function of heart rate measured after 10 min of coronary occlusion. Each bar represents the arrhythmia incidence of the corresponding 10 beat/min subgroup shown on the horizontal axis. Number of dogs in each subgroup is shown at the top of the corresponding bar. The data for control dogs were also depicted in figure 3. Although the numbers in each subcategory are small, a test of cumulative probability revealed a statistically significant (P < 0.05) overall deleterious action of atropine.
Table 1

<table>
<thead>
<tr>
<th>Mean Heart Rates (beats/min) during Studies</th>
<th>Preocclusion*</th>
<th>10 min postocclusion* (prior to treatment)</th>
<th>60 min postocclusion* (prerelease)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atropine studies</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Control (N = 27)</td>
<td>69 ± 3</td>
<td>81 ± 4</td>
<td>68 ± 4</td>
</tr>
<tr>
<td>Atropine treated (N = 28)</td>
<td>71 ± 2</td>
<td>88 ± 5</td>
<td>109 ± 2</td>
</tr>
<tr>
<td>Vagal stimulation studies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal heart rate (N = 26)</td>
<td>90 ± 4</td>
<td>104 ± 4</td>
<td>91 ± 1</td>
</tr>
<tr>
<td>Bradycardia (N = 24)</td>
<td>83 ± 4</td>
<td>98 ± 4</td>
<td>51 ± 1</td>
</tr>
</tbody>
</table>

* = SE.

Vagal Stimulation Studies

Because of the stratification procedure described in the Methods section, the differences in 10-min postocclusion heart rate between normal heart rate and bradycardia groups were not significant. In both groups the average 10-min postocclusion heart rate tended to be higher than analoguous values obtained during the atropine studies (table 1), probably reflecting the greater surgical trauma and sedative requirement of animals in the vagal stimulation studies.

When the results of 24 dogs with vagally induced bradycardia and 26 dogs with normal heart rates are compared (fig. 6) a nearly equal frequency of occurrence is observed for occlusion arrhythmias with long R′R′ arrhythmias, with short R′R′, VF, and for the overall incidence of occlusion ventricular arrhythmias. Similar results are found when arrhythmias developing within 10 min of release of the hour-long occlusion are examined (fig. 6).

Thus, our data indicate that vagally mediated bradycardia does not increase the incidence of serious ventricular arrhythmias during anterior myocardial ischemia in the normotensive dog. The 15 animals in the subgroup with collateral ligation had the same incidence and distribution of arrhythmias as the 35 members of the subgroup without collateral ligation.

Because the R′R′ categories (i.e. <0.43 sec and ≥0.43 sec) were derived from studies in which heart rates were normal or moderately elevated, they may not apply with equal validity when heart rate is reduced. As shown in figure 7, however, a detailed analysis of the minimum R′R′ for each dog revealed no difference in the distribution of minimum R′R′ between bradycardia and normal heart rate groups. A similar analysis using R′R′/QT (fig. 8) also showed that the bradycardia and normal heart rate groups were indistinguishable, thus excluding the possibility in our preparation that VPCs with a given R′R′ may fall nearer the T wave during bradycardia.

![Figure 6](http://circ.ahajournals.org/)

Incidence of each type of ventricular arrhythmia during acute coronary occlusion and following release of occlusion for 26 dogs (black) with normal heart rates (80–100 beats/min) and for 24 dogs (stipple) with vagally induced bradycardia (40–60 beats/min). The scheme of categorization is the same as that used in figure 1. Number of dogs in each category is shown at the bottom of the corresponding bar. None of the differences depicted here approached statistical significance.
Figure 7
Minimum coupling interval (R-R') of occlusion VPC's and VT observed in dogs with normal heart rate (left) and dogs with bradycardia (right). Mean R-R' in each group is indicated by a horizontal line. One dog in the bradycardia group with R-R' > 0.43 is not represented because precise information was not available from tape recordings. In the one animal developing ventricular fibrillation, a minimum R-R' was obtained from antecedent VPC's.

To further characterize the serious arrhythmias occurring during bradycardia and normal heart rates, we analyzed the time course of arrhythmia onset and termination during the entire 1-hour period of coronary occlusion in all dogs experiencing serious arrhythmias during occlusion (fig. 9). Serious ventricular arrhythmias were evident in five of eight members of the control group during the last 15 min of occlusion. In contrast, these arrhythmias showed a significant ($P < 0.05$) tendency to disappear in the bradycardia group during the last 15 min of occlusion. Moreover, in one animal with arrhythmia shortly after occlusion, the arrhythmia disappeared 4 min after heart rate was slowed and no serious ventricular arrhythmias returned during the remaining period of occlusion. Thus it is possible that bradycardia may exert a protective effect which requires time to become manifest.

Figure 8
Minimum value of RR'/QT attained during occlusion VPC's and VT in dogs with normal heart rate (left) and in dogs with bradycardia (right). Mean RR'/QT in each group is indicated by a horizontal line. As in figure 7, one dog in the bradycardia group is omitted for lack of precise data; and one dog with eventual VF had minimum RR'/QT selected from antecedent VPC's.

Discussion
Our study has attempted to elucidate the influence of heart rate and, in particular, the significance of vagally mediated bradycardia during the early phases of acute myocardial infarction from two points of view: (1) in terms of pathophysiology, do slower heart rates, especially those below 60 beats/min predispose to serious ventricular arrhythmias and death; and (2) with regard to potential therapy, does increasing the heart rate with prophylactically administered atropine tend to reduce the occurrence of serious arrhythmias during the early phases of acute myocardial infarction?

Information bearing on the first question may be derived from both phases of our study. Data from the control group of the atropine studies showed that spontaneously slower heart rates occurring during myocardial ischemia did not increase the occurrence of more serious ventricular arrhythmias (fig. 2). On the contrary, incidence of arrhythmias was directly related to early postocclusion heart rate (fig. 3). This direct relation between heart rate and incidence of arrhythmias was most dramatically
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Time course of serious arrhythmia (in this context, VPC's and VT with coupling interval < 0.43 sec) in those eight dogs of the normal heart group (upper panel) and those seven dogs of the bradycardia group which showed serious arrhythmias at any time during coronary occlusion. Shaded portions of each horizontal bar depict times when serious arrhythmias were present in each individual dog. The vertical dashed line indicates the 10-min point when heart rate control was initiated. One animal died (VF) 36 min after occlusion. Of the six dogs in the bradycardia group alive between 45 and 60 min, none had serious arrhythmias, in contrast to 5/8 of the control group with serious arrhythmias persisting into the last 15 min of occlusion. Moreover, one animal in the bradycardia group (lower panel, fourth from top) had serious arrhythmia before but not after vagal bradycardia. In a second animal (lower panel, fifth from top), serious arrhythmia disappeared soon after initiating vagal bradycardia.

manifested by animals with the lowest spontaneous rates (fig. 4): none of the animals with bradycardia (heart rate below 60 beats/min) had serious arrhythmias, in contrast to a 53% incidence of serious arrhythmia and 13% incidence of VF in animals without bradycardia. While these data may reflect a protective effect of bradycardia, it is also true that the lower heart rate may not be causally related to the reduced incidence of serious arrhythmias; both may reflect a relatively mild ischemic insult. It therefore seemed desirable to evaluate the influence of heart rate on the incidence of serious arrhythmias independently of the severity of myocardial ischemia. Furthermore, we wished to explore the effects of a more consistent and profound degree of bradycardia than that observed spontaneously. The vagal stimulation study accomplished both these objectives: severity of ischemia, as reflected by 10-min postocclusion heart rate, was randomized; and sustained, vagally mediated bradycardia was produced in half the animals by means of electrical stimulation of the cervical vagi. Under these circumstances the frequency of each type of ventricular arrhythmia was indistinguishable for dogs with heart rates between 40 and 60 beats/min and for those with heart rates between 80 and 100 beats/min (fig. 6). Thus, there was no evidence that vagally mediated bradycardia per se (in this instance, a consistent and moderately severe bradycardia) predisposed to serious ventricular arrhythmia. In fact, our data suggested that vagally mediated bradycardia may have exerted a protective effect during the last 15 min of occlusion (fig. 9).

With regard to a possible prophylactic therapeutic approach, our data suggest that atropine is not effective in preventing serious ventricular arrhythmias during the early phases of acute myocardial infarction. On the contrary, atropine significantly increased the incidence of close-coupled ventricular arrhythmias as well as the total incidence of arrhythmias during coronary occlusion (fig. 1). It also tended to increase VF, a finding that may be particularly important in view of several very recent reports describing VF developing after atropine administration to patients with acute myocardial infarction. It should be emphasized that atropine tended to exert a deleterious effect, regardless of pretreatment heart rate (and presumably, irrespective of the extent of ischemic insult). Thus, when matched to control animals with equal 10-min postocclusion (pretreatment) heart rates, each subgroup of atropine animals had a consistently higher incidence of serious occlusion arrhythmias (fig. 5).

In a clinical setting, situations unquestionably arise in which atropine should be administered promptly. In particular, patients with marked bradycardia and hypotension fall into this group (although there may be alternative methods of treatment even for some of these individuals). A detailed discussion of considerations bearing on the clinical use of atropine during acute myocardial infarction has been presented elsewhere. To summarize, experimental and clinical data indicate a cautious approach whenever atropine administration is contemplated for any patient with acute myocardial infarction unless the patient also has severe bradycardia and hypotension.

The tendency of atropine to predispose to arrhythmias occurring during ischemia can be
explained, at least in part, by the results of previous investigations. Thus, in either the closed-chest or open-chest dog, increasing heart rate during acute coronary occlusion augments the degree of myocardial ischemia, even when heart rate is increased from levels as low as 30 beats/min. If it can be assumed that the probability of serious arrhythmia is directly related to the degree of associated ischemic injury, then simple intensification of ischemia by the augmented heart rate could contribute to the deleterious arrhythmic actions of atropine. This hypothesis is strengthened by our recent finding that increasing heart rate during myocardial ischemia causes electrophysiologic changes indicative of greater electrical instability of the ventricle. Moreover, we found that vagal stimulation per se (independent of heart rate) increases ventricular electrical stability (as measured by VF threshold) in both nonischemic and ischemic hearts. In addition, Bailey and co-workers have shown that acetylcholine depresses the slope of diastolic depolarization, and increases the rise time, amplitude, and conduction velocity of action potentials recorded in the proximal portion of the His-Purkinje system of the canine ventricle. Thus, in addition to its heart rate-mediated effects, atropine also may increase the incidence arrhythmia by attenuating a stabilizing vagal influence. A third potential mechanism responsible for the arrhythmogenic influence of atropine was suggested by Scherlag and co-workers. These authors postulated that reentrant arrhythmias are more likely to occur when a greater number of supraventricular impulses (a necessary consequence of effective treatment with atropine) encounter delays, decremental conduction, or local block within a partially depolarized ischemic area.

Although atropine may predispose to ventricular arrhythmias by increasing the degree of ischemic injury and favoring reentry mechanisms, the drug might have been expected to favorably alter the outcome of acute myocardial infarction by overdrive suppression of ventricular arrhythmias. It has recently become clear, however, that not all types of ventricular arrhythmia need be considered harbingers of VF and death. Moreover, experimental data indicate that the mere abolition of a ventricular arrhythmia by a therapeutic intervention is not synonymous with therapeutic efficacy. In this regard, we have observed recently that atropine was highly effective in abolishing less serious arrhythmias during coronary occlusion but it was much less effective in abolishing those arrhythmias associated with eventual development of VF.

Obviously, our results are not necessarily directly applicable to the clinical situation because of the differences between our experimental model and acute myocardial infarction in man. In particular, posterior infarction in man frequently leads to vagally mediated bradycardia, while the ischemic zone in our canine model was always anterior. The precise influence of infarct site on occurrence of arrhythmias is uncertain. Differences in coronary arterial distribution to the canine conduction system preclude an exact canine replica of posterior infarction in man. A second potentially important difference from the clinical situation is the absence of hypotension in our experimental model. Our model was chosen expressly to avoid secondary arrhythmogenic actions associated with hypotension in order to clarify the primary actions of heart rate and atropine. However, some degree of hypotension commonly occurs in association with bradycardia during the early phases of acute myocardial infarction in man. It is not clear how often this hypotension per se leads to serious sequelae. Therefore, whether the overall benefit derived from a tachycardia-induced increase in blood pressure is sufficient to counterbalance possible arrhythmogenic and ischemic actions of atropine, thereby increasing survival in man, remains to be determined.

In addition to limitations imposed by the canine model, our conclusions may also be influenced by the diazepam used for sedation. Although an antiarrhythmic action has been suggested for diazepam, such an action was not found by other investigators. Moreover, the rather high incidence of serious arrhythmias in almost all groups of the present study also suggests that diazepam does not exert a potent antiarrhythmic influence. Chlorobutanol, a chloroform derivative, was present in small amounts (0.5%) in the atropine solution used and conceivably may have played a role in the adverse effects noted. If so, it should be noted that this chemical is present in the same amount in atropine solutions used clinically.

Despite its differences from the clinical setting, the animal model has certain unique advantages in ascertaining the results of coronary occlusion. For example, one can rigidly control therapy and other conditions from the very onset of ischemia. Therefore, data obtained in animal studies should fur-
nish significant supplementary information even though they cannot supplant clinical information.

In conclusion, our results indicate that neither spontaneously slow heart rates nor sustained bradycardia produced by electrical stimulation of the vagi caused an increase in serious arrhythmias during acute myocardial infarction in a closed-chest canine model. On the other hand, atropine administration in this setting produced a significant increase in serious ventricular arrhythmias during coronary occlusion. Although these results may not be directly applicable to man, our data indicate that further study is necessary before it can be assumed that vagally mediated bradycardia per se increases the risk of serious arrhythmia or, conversely, that speeding the heart rate with atropine diminishes the risk of serious arrhythmia in patients during the early phases of acute myocardial infarction.

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